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## Does Cardiac Resynchronization Therapy Benefit Patients With Right Bundle Branch Block

### *Cardiac Resynchronization Therapy Has a Role in Patients With Right Bundle Branch Block*

Angelo Auricchio, MD, PhD; Joost Lumens, PhD; Frits W. Prinzen, PhD

Cardiac resynchronization therapy (CRT) has been established as a useful therapy for patients with heart failure with abnormal QRS duration and low ejection fraction (EF). Although the vast majority of patients treated with CRT have a left bundle branch block (LBBB) QRS morphology, since the introduction of CRT into clinical practice, a growing number of patients with right bundle branch block (RBBB) QRS morphology or diffuse intraventricular conduction abnormality have been treated.<sup>1-19</sup> As shown in Table 1, the most recently conducted studies report a variable proportion of patients with RBBB  $\leq 18\%$ . Thus, these patients represent a sizeable subgroup in need of adjunct therapies on top of the best pharmacological therapy. This percentage is most likely an underestimation of the true number of patients with heart failure and RBBB, because CRT in patients with RBBB has been controversial from the beginning, although QRS widening  $\geq 120$  ms was the only ECG selection criterion for CRT. More recently, several studies have shown that non-LBBB patients benefit less from CRT than those with LBBB.<sup>20,21</sup> As a consequence, European Society of Cardiology guidelines indicate the use of CRT in non-LBBB patients with a QRS duration  $>150$  ms at class IIa/level of evidence B, whereas guidelines suggest the use of CRT in non-LBBB patients with a QRS duration between 120 and 150 ms at a lower recommendation class (class IIb, level of evidence B).<sup>22</sup>

Although several factors may be held accountable for the diverse response to CRT in RBBB compared with LBBB, they have not been systematically reviewed. However, several retrospectively conducted studies have suggested that CRT may be beneficial in subgroups of patients with RBBB. In the present article, we are taking a mechanistic approach to evaluate the effect of CRT in patients with heart failure diagnosed with RBBB. Thus, we will review the electrophysiological findings, the mechanical abnormalities observed in patients with RBBB, and finally the clinical results of CRT in this patient subgroup to address a key question: is RBBB an inappropriate indication for CRT or is CRT applied in the wrong way in patients with RBBB?

#### **Right and Left Ventricular Electric Activation in Patients With RBBB**

The relative fragility and mechanical structure of the right-sided conduction system may explain the high incidence of this conduction delay in the general population without evidence of structural heart disease. In the Framingham study, RBBB and LBBB developed in 70 and 55 patients, respectively, during 18-year follow-up in 5826 healthy individuals.<sup>23</sup> The Moli-sani study, which recruited 24 090 subjects in the central-southern region of Italy,<sup>24</sup> reported that RBBB was recorded in 589 individuals (2.44%), whereas LBBB was recorded in 181 individuals (0.75%); interestingly, RBBB was more frequent in men (3.4%) than in women (1.0%), whereas LBBB was slightly more frequent in women (0.9%) than in

#### **Response by Kenneth Bilchick on p 542**

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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**Table 1. Proportion of Patients With Conduction Abnormality Included in Selected Prospective and Observational Cardiac Resynchronization Therapy Studies**

| Study                           | Year of publication | NYHA Class | Mean LVEF | Mean QRS Duration | Total number of patients | Proportion of patients with conduction abnormality |      |      |
|---------------------------------|---------------------|------------|-----------|-------------------|--------------------------|--|------|------|
|                                 |                     |            |           |                   |                          | LBBB   | RBBB | IVCD |
| Prospective randomized studies* |                     |            |           |                   |                          |  |      |      |
| PATH-CHF I <sup>1</sup>         | 2002                | 3–4        | 21±6      | 174±30            | 42                       | 93%  | 7%   | 0%   |
| PATH-CHF II <sup>2</sup>        | 2003                | 2–4        | 23±7      | 155±20            | 86                       | 88%  | 5%   | 6%   |
| CONTAK CD <sup>3</sup>          | 2003                | 2–4        | 21±7      | 155±27            | 490                      | 54%  | 14%  | 33%  |
| MIRACLE <sup>4</sup>            | 2004                | 3–4        | 22±6      | 166±21            | 453                      | 80%  | 11%  | 9%   |
| MIRACLE ICD II <sup>5</sup>     | 2004                | 2          | 25±7      | 166±24            | 186                      | NA   | 17%  | NA   |
| COMPANION <sup>6</sup>          | 2004                | 3–4        | 22        | 158               | 1520                     | 71%  | 11%  | 18%  |
| CARE-HF <sup>7</sup>            | 2005                | 3–4        | 25†       | 160†              | 813                      | 94%  | 5%   | 1%   |
| REVERSE <sup>8</sup>            | 2008                | 1–2        | 26±7      | 151±23            | 680                      | 54%  | 8%   | 19%  |
| MADIT-CRT <sup>9</sup>          | 2009                | 1–2        | 24±5      | 152±18            | 1817                     | 70%  | 13%  | 17%  |
| RAFT <sup>10</sup>              | 2010                | 2–3        | 23±5      | 158±24            | 1866                     | 69%  | 9%   | 11%  |
| Observational studies*          |                     |            |           |                   |                          |  |      |      |
| Wokhlu <sup>11</sup>            | 2009                | 2–4        | 23±7      | 158±31            | 338                      | 67%  | 11%  | 13%  |
| Adelstein <sup>12</sup>         | 2009                | 3–4        | 23±9      | 175±30            | 636                      | 64%  | 9%   | NA   |
| Rickard <sup>13</sup>           | 2010                | 2–4        | 22±8      | 156±20            | 335                      | 61%  | 11%  | 28%  |
| Bilchick <sup>14</sup>          | 2010                | 1–4        | 23±6      | 157±26            | 14946                    | 69%  | 11%  | 20%  |
| Varma <sup>15</sup>             | 2011                | 2–4        | 23±8      | 163±21            | 120                      | 45%  | 26%  | NA   |
| Leong <sup>16</sup>             | 2012                | 3–4        | 26±8      | 161±19            | 561                      | 84%  | 16%  | 0%   |
| Hara <sup>17</sup>              | 2012                | 3–4        | NA        | 160±26            | 254                      | 50%  | 18%  | 32%  |
| Kandala <sup>18</sup>           | 2013                | 3–4        | 23±6      | 156±28            | 144                      | 57%  | 13%  | 30%  |
| Survey*                         |                     |            |           |                   |                          |  |      |      |
| Dickstein <sup>19</sup>         | 2009                | 1–4        | 27±8      | 157±32            | 2438                     | 68%  | 6%   | NA   |

CARE-HF indicates Cardiac Resynchronization-Heart Failure; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; ICVD, intraventricular conduction disturbance; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MADIT-CRT, Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; MIRACLE, Multicenter InSync: Randomized Clinical Evaluation; MIRACLE II, Multicenter InSync ICD II: Randomized Clinical Evaluation; NA, not available; NYHA, New York Heart Association; PATH-CHF I, Pacing Therapies in Congestive Heart Failure I; PATH-CHF II, Pacing Therapies in Congestive Heart Failure II; RAFT, Resynchronization-defibrillation for Ambulatory heart Failure Trial; RBBB, right bundle branch block; and REVERSE, Resynchronization reVerses Remodeling in Systolic left vEntricular dysfunction.

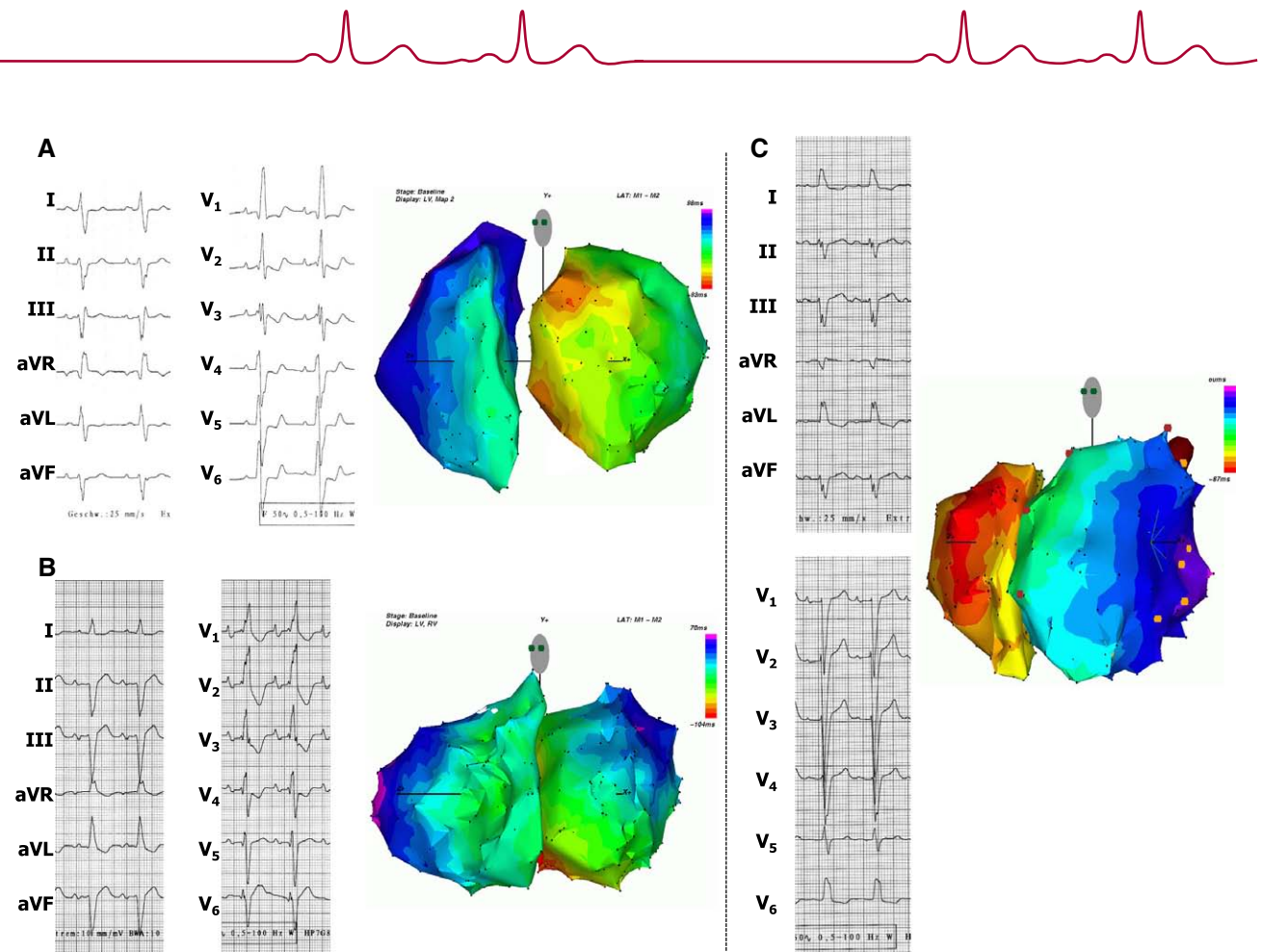
\*Prospective randomized controlled studies are reported using the respective acronym, whereas the observational studies and survey are reported according to the first author of the published article.

†Median value instead of mean value has been reported.

men (0.6%). Furthermore, new onset of RBBB in patients with heart disease may be indicative of aggravation of the heart condition<sup>25</sup> and possible association with right ventricular (RV) dysfunction of primary or secondary origin.

Insight into electric activation during LBBB and during ventricular pacing (including CRT) has steadily increased during the past years. In contrast, detailed 3-dimensional mapping in patients with RBBB is limited to a single case series published by Fantoni et al<sup>26</sup> in 2005. These authors performed extensive measurement of both RV and left ventricular (LV) endocardial electric activation in heart failure patients with RBBB and LBBB. In heart failure patients with RBBB, the earliest ventricular activation site is located in the LV myocardium,

usually in the septum. The LV septal activation coincides with the beginning of the QRS complex. After a considerable delay (50–70 ms), the activation arrives at the RV side of the septum because of slow left-to-right transseptal activation. The electric activation of the entire RV occurs slowly, most likely as a result of cell-to-cell conduction: from the septal breakthrough site, the activation front proceeds toward the RV anterior wall and then to the right lateral wall and the outflow tract, which both are the latest activated regions. Because of this activation pattern, RV anterior and lateral regions are delayed with respect to the onset of the QRS complex, thus mirroring on the right side of the heart the pattern that is usually observed in the LV of patients with LBBB (Figure 1). As a result, total



**Figure 1.** Electroanatomic mapping and surface 12-lead ECG in a patient with right bundle branch block (RBBB; **A**), in a patient with RBBB masking left bundle branch block (LBBB; **B**), and in a patient with LBBB (**C**). The activation sequence is color-coded by 10-ms isochrones (red indicates the earliest activation region, and purple indicates the latest activation region).

RV endocardial activation time in patients with RBBB is much longer (80–120 ms) than in patients without conduction delays (50–80 ms). Because in RBBB much or all of the RV undergoes depolarization after activation of the LV has been completed, the electric forces generated by the RV are not masked by the predominant and largest LV electric forces but now show up as a delayed component in the QRS complex, drawing the characteristic RBBB morphology in the surface ECG (Figure 1).

In some heart failure patients with RBBB, the QRS morphology is significantly different from the characteristic RBBB appearing in otherwise structurally normal hearts. These patients with heart failure show a specific electrocardiographic pattern defined by Rosenbaum et al<sup>27</sup> as RBBB masking LBBB, characterized by a broad, slurred, sometimes notched R wave on leads I and aVL, together with a leftward axis deviation frequently noted in LBBB QRS morphology patients as well (Figure 1). In patients with RBBB masking LBBB, electroanatomic mapping data have demonstrated that not only RV activation is abnormally delayed but also LV activation is delayed as much as in patients presenting with LBBB.<sup>26</sup> Furthermore, the LV activation pattern observed in these patients resembles the one observed in patients with LBBB (Figure 1). Notably, patients with heart failure presenting with pure RBBB differed

from those with RBBB masking LBBB by presenting an LV anterobasal breakthrough in addition to the septal one (Figure 1). Patients with RBBB masking LBBB usually present with a severe biventricular postischemic cardiomyopathy, with large myocardial injury because of significant lesion of the anterior descending coronary artery.

### RV and LV Mechanical Abnormalities in Animals and Patients With RBBB

Canine studies using experimental LBBB have shown that this intervention immediately and persistently reduces LV pump function.<sup>28,29</sup> In this regard, less is known about the hemodynamic effect of RBBB. In the 1980s, Yasui et al<sup>30</sup> induced experimental RBBB in dogs with normal hearts and in dogs with moderate and severe RV hypertrophy. They found minor influence of RBBB on RV and LV pump function in normal hearts, but significant deterioration if occurring in hearts with RV hypertrophy: RBBB increased RV end-diastolic pressure, RV  $dP/dt_{max}$ , and stroke volume. This deterioration was related to the duration of the QRS complex.<sup>30</sup> In this model, LV function was hardly affected. These data are important because they indicate that RBBB may affect RV function, the forgotten ventricle; however, few data are available on RV systolic

function in patients with heart failure, alone or in combination with RBBB, LBBB, and CRT. However, it is important to notice that RV hypertrophy is rarely observed in adults patients with systolic heart failure; therefore, it makes it difficult to completely translate in patients the observation by Yasui et al.<sup>30</sup>

Byrne et al<sup>31</sup> investigated mechanical dyssynchrony in a canine model of RBBB and LBBB in combination with tachypacing-induced heart failure. With LBBB, there was a septal shortening and lateral stretch during early systole followed by septal stretch and lateral shortening later in systole. However, with RBBB, strain was more uniform with little dyssynchrony in early systole and posteroseptal shortening in late systole without reciprocal stretch. Plots of instantaneous strain versus short-axis segment location (representing an instantaneous distribution of strain throughout all myocardial segments at 2 different time points in the cardiac cycle) showed a more sinusoidal strain profile during early systole in the LBBB model, reflecting a larger disparity of strains. For the RBBB case, segment-to-segment variation was noted in late systole but was lower in magnitude than that seen with LBBB. Early systolic strain distribution in RBBB was nearly uniform.<sup>31</sup>

In heart failure patients with RBBB with an indication for CRT, the mechanical abnormalities of right and left ventricle have been rarely reported.<sup>17,32</sup> Hara et al<sup>17</sup> examined 278 patients with heart failure with any kind of ventricular conduction disturbance and compared the echocardiographic characteristics (assessment of interventricular mechanical delay and speckle-tracking radial strain) with outcome after CRT. Patients with LBBB had the most prevalent and significant degree of radial strain dyssynchrony compared with non-LBBB patients, and patients with RBBB had the least dyssynchrony, even if QRS duration was comparable in patients with LBBB and RBBB. In patients with LBBB, peak radial strain occurred earlier in the anteroseptum and later in the posterior wall than in non-LBBB patients. LV pre-ejection delay and interventricular mechanical delay were greatest in patients with LBBB, but RV pre-ejection delay was greatest in patients with RBBB, whereas the interventricular mechanical delay was usually small in patients with RBBB. All these data indicate minor LV involvement in many patients with RBBB but indeed possible involvement of RV function. Importantly, 17 of 45 patients with RBBB did show LV radial strain dyssynchrony (>130 ms), which might be associated with left anterior hemiblock or other LV conduction abnormalities on top of the RBBB.

### Outcome of Patients With RBBB

Morbidity and mortality of heart failure patients with RBBB QRS pattern are high, although comparative data from epidemiological studies show a slightly better prognosis for patients with RBBB than for patients with LBBB. The Italian Network on Congestive Heart Failure Registry included 5517 patients with heart failure of different causes.<sup>33</sup> Data derived from the Italian Network on Congestive Heart Failure database showed that the total 1-year mortality in patients with RBBB was equal to that in patients with narrow QRS complex (11.9%), yet significantly lower than in patients with LBBB (16.1%); notably,

patients with RBBB more frequently presented with heart failure of ischemic cause, whereas primary dilated cardiomyopathy was the most frequent cause of heart failure in patients presenting with complete LBBB. Furthermore, outpatients with complete RBBB were older and more frequently had cardiac enlargement and a reduced EF, but RBBB was not correlated with a more symptomatic heart failure. Similarly, data from the Enhanced Feedback for Effective Cardiac Treatment (EFFECT) study showed that LBBB and RBBB conferred an increased unadjusted risk of adverse outcomes, but LBBB was the only significant predictor of death in 1 and 5 years.<sup>34</sup>

The most compelling data about absolute and relative lower hospitalization rate and death rate in heart failure patients with RBBB compared with LBBB have been recently published by Zareba et al<sup>20</sup> for the implantable cardioverter-defibrillator (control) group of the Multicenter Automatic Defibrillator Implantation Trial With CRT (MADIT-CRT) study. Notably, MADIT-CRT patients differed from the Italian Network on Congestive Heart Failure Registry patients because they had a lower functional class (New York Heart Association class I or II), had no history of atrial fibrillation, and had no previous major ventricular arrhythmias. The MADIT-CRT investigators presented cumulative probabilities of primary end points, consisting of heart failure event or death, and the secondary end point of death in each conduction groups and according to device type. The patients with LBBB had a nonsignificantly higher risk of primary end points at 3 years compared with the patients with RBBB and intraventricular conduction disturbance (32% versus 19% versus 23%, respectively), a difference that was mainly driven by differences in heart failure events (Figure 2). Interestingly, the risk of the combined end point of either ventricular tachycardia or ventricular fibrillation requiring appropriate therapy or death was not different between LBBB (31%) and RBBB (28%; Figure 2).

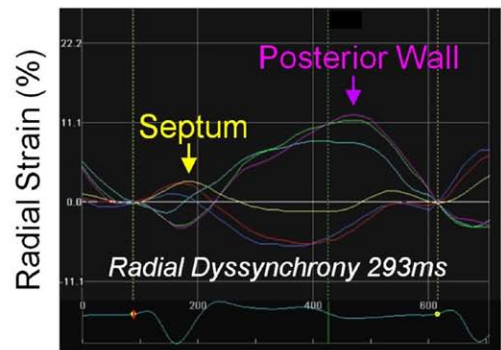
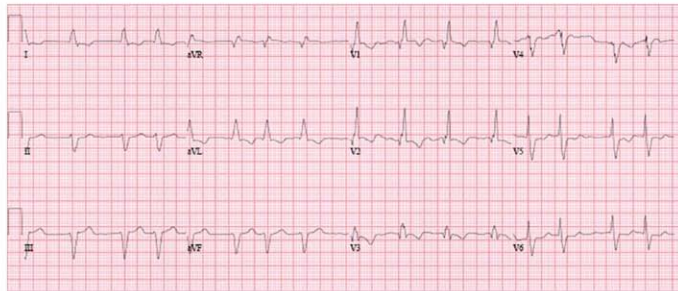
### CRT in a Preclinical RBBB Model

The differential effect of biventricular pacing in the preclinical setting of RBBB or LBBB has been reported by Byrne et al.<sup>31</sup> These investigators showed that the improvement in synchrony (and function) with CRT in hearts with RBBB was less than in those with LBBB. In the acute setting, both LV  $dP/dt_{max}$  and stroke work increased by 5% to 10% in the RBBB hearts, which is less than half of the increase in LBBB hearts.<sup>35,36</sup> Notably, the mode of CRT did not necessarily require biventricular stimulation. Single-site RV pacing produced similar improvements in global mechanical function and synchrony as with biventricular pacing. Interestingly, significant narrowing of the QRS complex with both RV-only and biventricular pacing did not translate to a large functional improvement. These findings are reminiscent of the effects of biventricular and LV pacing in LBBB hearts, supporting the idea that in CRT pacing of the latest activated ventricle dominates its benefit. An important observation was that RV and biventricular pacing also, more prominently, improved RVEF, suggesting that CRT with underlying RBBB may especially involve improvement of RV function.

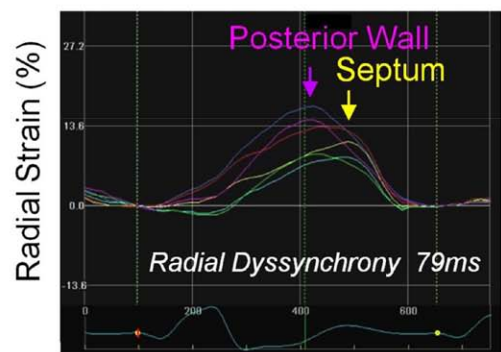
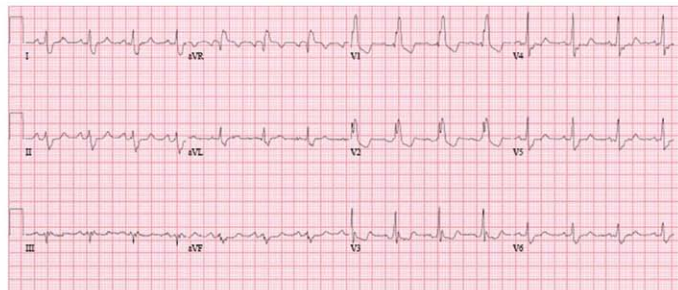


**A RBBB: Significant Radial Dyssynchrony**

Long-term survivor; EF improved from 17% to 40% after CRT.

**B RBBB; No Significant Radial Dyssynchrony**

No Change in EF; patient died 2 months after CRT.



**Figure 2.** Two patient examples of different right bundle branch block (RBBB) morphology (**A**, RBBB masking left bundle branch block [LBBB]; **B**, RBBB without LBBB) and radial strain dyssynchrony, with ejection fraction (EF) response and long-term outcome after cardiac resynchronization therapy (CRT). Reproduced from Hara et al<sup>17</sup> with permission of the publisher (Oxford University Press, 2012).

**CRT in Patients With RBBB**

During the past 10 years, there have been some observational studies in patients with RBBB, most of them including  $\leq 100$  patients, which assessed the effect of CRT on some surrogate end points of mortality and few on morbidity and mortality directly. Rickard et al<sup>13</sup> observed that patients with RBBB who received CRT derived less cardiac reverse remodeling and less symptomatic improvement compared with patients with LBBB. Egoavil et al<sup>37</sup> followed up 61 patients with RBBB randomly assigned to CRT or no CRT and found no improvement in aerobic capacity (measured by maximal oxygen consumption) after 6 months. Wokhlu et al<sup>11</sup> and Adelstein and Saba<sup>12</sup> demonstrated that patients with RBBB receiving CRT had a higher mortality rate and increased progression of heart failure (to transplant or assist device implantation) compared with patients with LBBB.

More recently, the results of 2 large US registries including patients with LBBB, intraventricular conduction disturbance, and RBBB have been published. Bilchick et al<sup>14</sup> used the data from the Medicare ICD Registry between 2005 and 2006 to characterize prognosis after CRT defibrillator (CRT-D) and to assess the relationship between clinical factors measured at the time of implantation and outcomes after CRT-D in  $\approx 15000$  Medicare patients.<sup>14</sup> In particular, they tested the hypothesis that patients with RBBB have significantly worse outcomes after CRT-D implantation than those with LBBB. Among all patients receiving CRT-D, RBBB morphology was among the most powerful predictors of outcome,

even after adjustment for QRS width and other covariates. RBBB had significantly higher short-term and long-term adjusted hazards for death among all patients with CRT-D. RBBB had twice the adjusted hazard for death (hazard ratio [HR], 1.99;  $P=0.001$ ) as LBBB. An even larger study also using Medicare data between 2006 and 2009 explored the outcome in 24 169 patients receiving CRT-D. This study showed that mortality was lowest in patients with LBBB and QRS duration  $>150$  ms and worse in LBBB with QRS duration of 120 to 149 ms (HR, 1.30) and even worse in patients with non-LBBB morphology with QRS duration  $>150$  ms (HR, 1.34) and 120 to 149 ms (HR, 1.52).<sup>21</sup>

As far as meta-analysis is concerned, Sipahi et al<sup>38</sup> performed a large meta-analysis on randomized CRT trials with a total of 5356 patients. Within this study, 1233 patients had non-LBBB conduction abnormalities that were randomly assigned to CRT or no-CRT, a size that is comparable with the major individual CRT trials such as Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) and Cardiac Resynchronization-Heart Failure (CARE-HF). They found that there was no trend for reduction in clinical events in this non-LBBB patient category. However, it is important to emphasize that this meta-analysis was of little value to establish the role of CRT in patients with RBBB because it was underpowered to estimate the clinical effects of patients with RBBB alone as evidenced by a relatively wide 95% confidence interval (0.69–1.20) for a meta-analytic HR.

Taken together, none of the observational studies and the meta-analysis published till date were able to demonstrate

a significant CRT benefit in patients with RBBB. However, if one considers the MADIT-CRT study results in the control arm, which showed a better outcome in RBBB than in LBBB patients but a larger mortality in RBBB CRT-treated patients than in LBBB CRT-treated patients observed in both Medicare registries, one may even think of an excess in mortality because of CRT in patients with RBBB.

### CRT in a Subset of Patients With RBBB

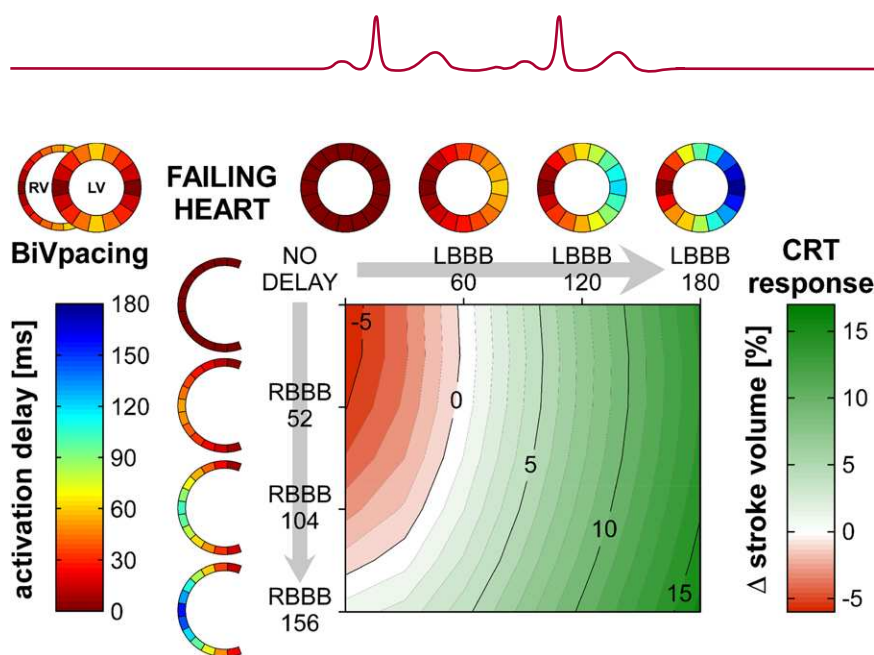
Having said this, all above does not completely rule out moderate improvements in subsets of patients with RBBB. Several studies have characterized such patient subsets, either by echocardiographic criteria or by specific ECG pattern. In one of the earliest case series, Garrigue et al<sup>39</sup> reported a beneficial response to CRT (eg, reduced LV end-diastolic diameter, decreased mitral regurgitation, and improved aortic time-velocity integer) but only in RBBB subjects with concomitant LV intraventricular dyssynchrony. Chandra et al<sup>40</sup> reported in 44 patients that the presence of concomitant left hemiblock among patients with RBBB referred for CRT was associated with greater response to therapy (defined as improvement in LVEF  $\geq 5\%$  or New York Heart Association class). Varma<sup>15</sup> studied the inferolateral LV activation delay, as measured by the distance between QRS onset and the intrinsicoid of the LV ECG in patients with LV dysfunction and RBBB versus LBBB. In that study, the QRS duration correlated well with the inferolateral LV activation delay in both groups, although somewhat more strongly in patients with LBBB. Therefore, at wider QRS durations, patients with non-LBBB morphologies are likely to have significant LV activation delay, an electric substrate amenable to resynchronization. Similarly, in a more recent study, it has been shown that in the subgroup of RBBB patients with mechanical dyssynchrony (radial strain) similar to those of the patients with LBBB, a much favorable response to CRT as given by death, implantation of ventricular assist device, and heart transplantation was found.<sup>17</sup> Also, the increase in LVEF and the reduction of end-systolic volume in patients with RBBB showing radial dyssynchrony were similar to that noticed in typical patients with LBBB. In contrast, those RBBB patients without significant radial dyssynchrony showed an unchanged LVEF and even a progression of LV remodeling process.<sup>17</sup> Kandala et al<sup>18</sup> have recently reported about the use of LV lead electric delay (LVLED), measured intraprocedurally as the interval between QRS onset on the surface ECG to the peak of sensed electrogram on LV lead. Among 144 patients, heart failure hospitalization was higher in non-LBBB compared with LBBB patients (43.5% versus 24%;  $P=0.015$ ). However, in both LBBB and non-LBBB patients, those with long LVLED had a lower heart failure hospitalization than those with short LVLED (36% versus 61%;  $P=0.026$ ). In adjusted Cox proportional hazards model, the long LVLED in LBBB and non-LBBB was associated with an improved outcome. Specifically, in non-LBBB, LVLED  $\geq 50\%$  of QRS duration was associated with improved event-free survival with respect to time to first heart failure hospitalization (HR,

0.34;  $P=0.011$ ) and composite outcome (HR, 0.41;  $P=0.019$ ). Finally, the most recent report by the MADIT-CRT investigator<sup>41</sup> found that subjects with RBBB without left anterior fascicular block experienced greater improvement in cardiac function after 12 months of CRT-D than those with left anterior fascicular block. In contrast, there was no difference in clinical outcomes (ie, death or heart failure admissions) between RBBB subjects with or without a left anterior fascicular block pattern on the surface ECG, despite significant improvements in cardiac function by echocardiography. Therefore, this study seems to run counter to the aforementioned studies, because a close reading of Figure 1 of Tompkins et al<sup>41</sup> shows that the patient presenting with left anterior fascicular block also has ECG features of the so-called RBBB masking LBBB by Rosenbaum et al<sup>27</sup>: broad, slurred, sometime notched R wave on leads I and AVL, with a leftward axis deviation. There is no clear explanation for these apparently opposite findings.

In previous studies, the CircAdapt model of the human heart and circulation ([www.circadapt.org](http://www.circadapt.org)) proved to be a useful tool to investigate the mechanism of CRT in heart failure patients with LBBB.<sup>42,43</sup> Here, we used the CircAdapt model to simulate CRT in the failing heart with different degrees of RBBB, LBBB, or with a combination of both conduction abnormalities. First, a simulation of a failing heart with decreased ventricular contractility and synchronous ventricular activation was obtained as described previously.<sup>43</sup> Second, different degrees of RBBB were simulated by imposing dyssynchronous RV free wall activation up to a maximal local activation delay of 156 ms. In addition, different degrees of (coexistent) LBBB were simulated by imposing a septal-to-lateral wall activation delay up to a maximum value of 180 ms. Finally, CRT was applied by imposing the same biventricular pacing protocol to all simulations as published previously by Lumens et al.<sup>43</sup> Figure 3 summarizes all the baseline activation sequences simulated and also illustrates the general activation pattern used for CRT. Furthermore, Figure 3 shows for all simulations the acute hemodynamic response to CRT, defined as the relative change of stroke volume with respect to baseline (63 mL). Table 2 summarizes global cardiac function during baseline and after CRT for the synchronous failing heart (NO DELAY) and for 3 dyssynchronous failing hearts (RBBB 156, LBBB 180, and RBBB 156 and LBBB 180). In general, these simulation data support the previously reviewed clinical observations that pure RBBB without LV electric dyssynchrony is not a substrate that should be treated with conventional CRT. Only when sufficient LV dyssynchrony substrate coexists, however, acute response to CRT increases to clinically relevant positive values.

### Implication for the Deployment of CRT in Patients With RBBB

After reviewing the available data on RBBB, there is a legitimate question to be addressed: is RBBB an inappropriate indication for CRT or is CRT applied wrong in patients with RBBB? The suitability of CRT for a patient subgroup, such as RBBB, is important because the therapy is relatively expensive and it comes with some potential complications.



**Figure 3.** Acute hemodynamic response to conventional biventricular (BiV) pacing in various computer simulations of a failing heart with synchronous ventricular activation, right bundle branch block (RBBB), left bundle branch block (LBBB), or a combination of RBBB and LBBB. Note that cardiac resynchronization therapy (CRT) hardly improves or even deteriorates cardiac pump function in hearts with RBBB in the absence of sufficient coexistent left ventricular (LV) activation delay. RV indicates right ventricular; and RVA, right ventricular apex.

More importantly, a CRT nonresponse may actually imply an adverse effect of the therapy on cardiac function.<sup>17</sup> After all, application of biventricular pacing in a heart with perfectly normal ventricular conduction widens QRS duration and reduces contractility.<sup>42</sup> Recent CRT studies in patients with narrow QRS complex support this view.<sup>44,45</sup> Because in isolated RBBB the LV conduction is normal, biventricular pacing may prolong LV activation and thus reduce LV function. In canine failing RBBB hearts, RV and biventricular pacing resulted in only minor acute improvements in LV function,<sup>31</sup> which may not justify the costs and risks of applying CRT. All these arguments support the opinion that RBBB is a wrong indication for CRT. Whether some pacing therapy may be beneficial by pacing at 1 (free wall of right ventricle) or multiple areas (free wall and outflow tract of right ventricle) of electric delay is unknown.

However, several factors strongly suggest that CRT is delivered in a wrong way in hearts with RBBB. Because RBBB

predominantly affects RV function, patients with poor RV function may benefit from CRT, and this is a virtually unstudied area. Furthermore, to create the best resynchronization in the RV, the commonly used pacing site (RV apex) may not be optimal because electroanatomic maps show that the RV lateral wall is latest activated.<sup>26</sup> Therefore, the benefit of implanting a pacing lead at a lateral site rather than at the apex should be investigated, together with the usefulness of pacing the RV outflow tract with a second lead. Although these possibilities improve the application of CRT in patients with RBBB, conventional CRT may be effective in the subgroup of patients with RBBB who also have a delayed LV activation. Therefore, we hypothesize that individualized treatment strategies shall be used based on the presence of LV and RV dyssynchrony demonstrated either by advanced echocardiographic techniques or by surface ECG. Admittedly, the proposed treatment options have been mechanistically developed (Figure 4), thus requiring confirmation in larger prospective studies. These studies should

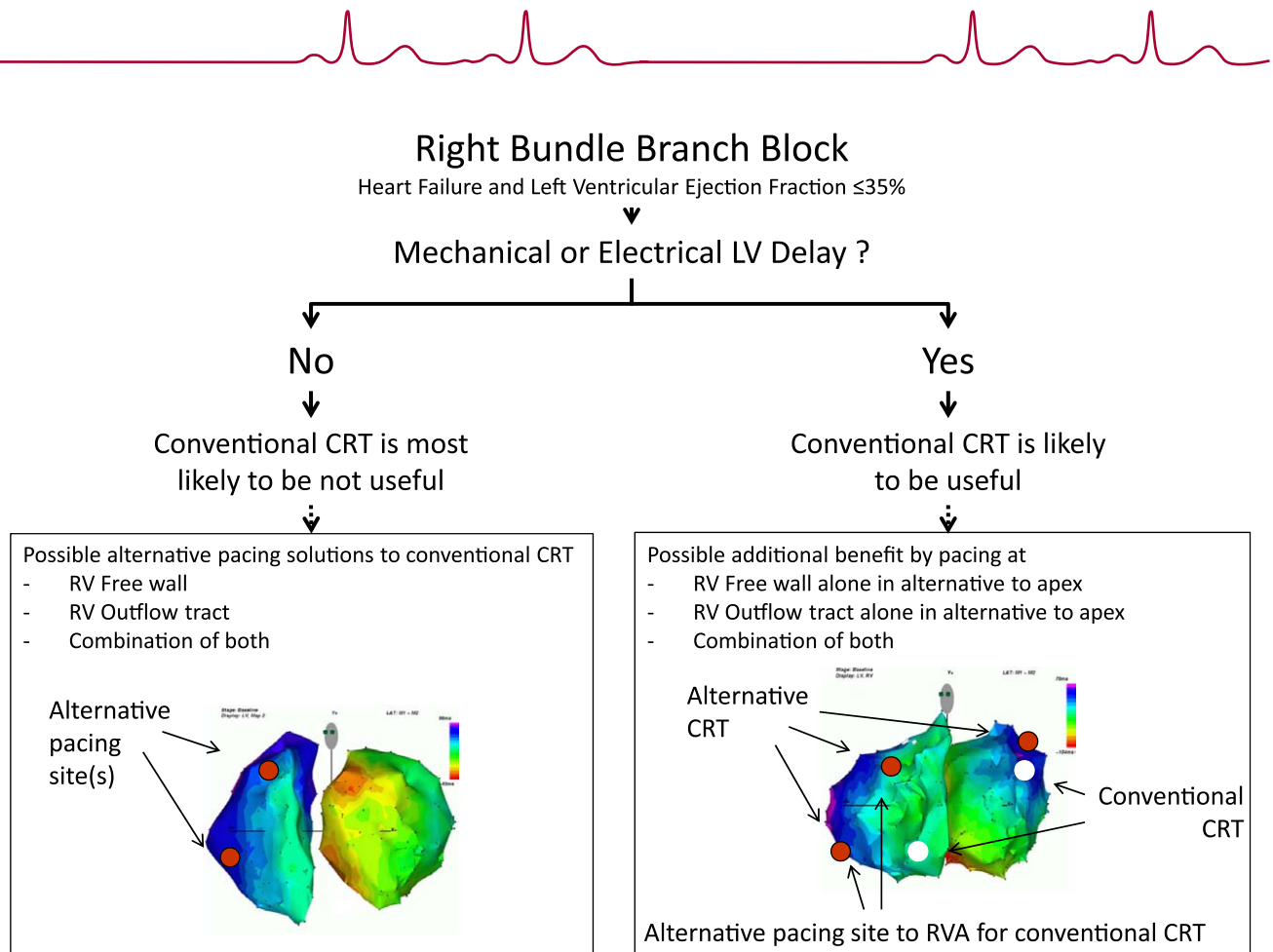
**Table 2. Global Cardiac Function During Baseline and After CRT for the Synchronous Failing Heart and for 3 Dyssynchronous Failing Hearts Presenting With RBBB and LBBB**

| Function Index | NO DELAY  |     | RBBB 156  |     | LBBB 180  |     | RBBB 156 and LBBB 180 |     |
|----------------|-----------|-----|-----------|-----|-----------|-----|-----------------------|-----|
|                | Baseline* | CRT | Baseline* | CRT | Baseline* | CRT | Baseline*             | CRT |
| HR, bpm        | 80        | 80  | 80        | 80  | 80        | 80  | 80                    | 80  |
| AV delay, ms   | 150       | 150 | 150       | 150 | 150       | 150 | 150                   | 150 |
| SV, mL         | 63        | 59  | 63        | 63  | 63        | 73  | 63                    | 75  |
| RVEF, %        | 38        | 37  | 36        | 36  | 28        | 33  | 29                    | 33  |
| LVEF, %        | 30        | 29  | 30        | 29  | 25        | 29  | 26                    | 29  |
| LVEDP, mm Hg   | 24        | 23  | 24        | 27  | 42        | 39  | 40                    | 40  |

The value of conduction delay within each ventricle is arbitrary and is indicated in milliseconds. AV delay indicates atrioventricular delay; CRT, cardiac resynchronization therapy; HR, heart rate; LBBB, left bundle branch block; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NO DELAY, synchronous failing heart; RBBB, right bundle branch block; RVEF, right ventricular ejection fraction; and SV, stroke volume.

\*Homeostatic control was active during all baseline simulations so that mean arterial pressure and cardiac output were constant (ie, 92 mm Hg and 5 L/min, respectively) in these simulations.





**Figure 4.** Mechanistically based flow chart indicating possible implantation strategies in cardiac resynchronization therapy (CRT) patients presenting with right bundle branch block and electric or mechanical activation delay of the left ventricle (LV). RV indicates right ventricular.

include detailed echocardiographic evaluation of both RV and LV function and strain analysis for patient selection as well as to better characterize the immediate, short-term, and long-term effect on cardiac mechanics of each of the proposed novel pacing configurations. Further tools that may support the mechanistic approach could be the determination of delay between Q wave and LV electrogram (Q-LV time; also known as LVLED) or even more elegantly using noninvasive electric mapping.<sup>46</sup> Obviously, simulation tools such as the CircAdapt model can also be used to investigate relative effectiveness of different pacing strategies in subsets of patients with heart failure.

## Conclusions

The available evidence indicates that straightforward application of CRT in patients with RBBB should be discouraged. However, additional studies should be performed as to whether a subset of patients with RBBB may benefit from CRT. For this purpose, a pooled analysis on individual patient data with RBBB QRS morphology from all recent major CRT trials (eg, MADIT-CRT, Resynchronization-defibrillation for Ambulatory heart Failure Trial [RAFT], Resynchronization reVERses Remodeling in Systolic left vEntricular dysfunction [REVERSE]) is urgently needed. The analysis should look at

hard and soft outcomes and also examine subsets within the RBBB population, including cause of underlying cardiomyopathy and presence of left fascicular block. The results of the analysis may then direct further research, perhaps indicating a need for randomized trials in such subsets of patients with RBBB. We acknowledge, however, the difficulty in conducting a trial in patients with RBBB because of the rarity of the population and the possibly long-term follow-up needed to demonstrate some differences between patients with LBBB versus RBBB and within the RBBB population. Alternatively and additionally, mechanistic studies are required to characterize the effect of resynchronization on systolic and diastolic function of right and left ventricles better with multiple RV leads or alternative RV/LV lead positions.

## Disclosures

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KEY WORDS: bundle-branch block ■ cardiac resynchronization therapy ■ heart failure

**Response to Angelo Auricchio, MD, PhD, Joost Lumens, PhD, and Frits W. Prinzen, PhD**

*Kenneth C. Bilchick, MD, MS*

In the companion paper, Auricchio et al have taken the position that cardiac resynchronization therapy (CRT) has a significant role in patients with heart failure (HF) and right bundle branch block (RBBB). This response will highlight the influence of left-sided conduction system disease on electric and mechanical activation in HF with RBBB and the impact of the CRT pacing strategy in these patients.

Physiological experiments in HF with RBBB without left-sided conduction system disease (pure RBBB) indicate that left ventricular (LV) free wall pacing is unlikely to improve hemodynamics in this situation. In fact, right ventricular pacing alone (without LV free wall pacing) has been shown to have potential benefits for both LV and right ventricular hemodynamics in HF with RBBB. This contrasts with the hemodynamic benefits demonstrated for LV free wall pacing in left bundle branch block (LBBB).<sup>2</sup> These physiological data are supported by large registry studies showing that patients with RBBB or non-LBBB have worse outcomes after CRT than patients with LBBB.

Despite these negative results for CRT in RBBB, there is still interest in whether it may be possible to identify a small subset of patients with RBBB who may benefit from CRT. In fact, coronary sinus recordings from the basal inferolateral LV in patients with HF have shown that some patients with RBBB have moderately prolonged electric timing in this area relative to QRS onset, although only patients with LBBB had activation times >160 ms in this region. A small electric mapping study provides insights into electric activation in the case of RBBB with concomitant left-sided conduction system or what has also been termed LBBB masquerading as RBBB. In this mapping study, the presence of only a single electric breakthrough site on the posterior LV septum (rather than both anterior and posterior breakthrough sites) in a patient with RBBB and left anterior fascicular block was associated with anterior LV activation timing that was about as late as the right ventricular free wall. In this regard, it is interesting that a subgroup analysis of the Multicenter Automatic Defibrillator Implantation Trial With CRT (MADIT-CRT) trial has shown that RBBB patients with left anterior fascicular block experience suboptimal outcomes compared with other patients with RBBB, such as those with concomitant left posterior fascicular block. It is possible that the latest activated sites in the patients with left anterior fascicular block were anterior and that the best LV pacing sites were not targeted for these patients. In any case, this highlights the potential use of advanced cardiac imaging for mapping electric and mechanical activation in patients with HF and non-LBBB.

In summary, both clinical and physiological studies for CRT in RBBB indicate that CRT as it is typically implemented is much less likely to improve outcomes in patients with HF associated with RBBB relative to patients having HF with LBBB. Additional studies that investigate novel ways to implement CRT in patients with RBBB and use advanced cardiac imaging hold promise for improving outcomes in patients with HF and non-LBBB conduction delays.



## Does Cardiac Resynchronization Therapy Benefit Patients With Right Bundle Branch Block: Cardiac Resynchronization Therapy Has a Role in Patients With Right Bundle Branch Block

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